COMMENTARY

Gut Check:
A Career in Colon Cancer Research

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(Photo: Courtesy of S. Markowitz)

Sanford Markowitz, M.D.

Working in the NCI-Navy Branch was a wonderful opportunity; the program attracted an extraordinarily talented group of people. John Minna's interest was in lung cancer, but the work he led became a roadmap for studying solid tumors. Back then, there were no disease models; one really had to start at the very beginning to create the cell lines and the tissue banks. The seminal cancer discoveries were being made in blood cancers, in part, because cells were readily available from a blood draw and many were easy to culture.

I had a long-standing interest in colon cancer for personal reasons. My father was diagnosed with the disease when I was an intern. So when I developed my own research agenda, it was natural to combine that personal motivation with ideas stimulated by my exposure to solid tumor research. The Case Western leadership, under Nathan Berger, M.D., was committed to building a solid tumor research program, making my appointment a natural fit.

One of the early successes of our program was the discovery that TGF-β receptors were tumor suppressor genes. We found a unique sequence in these receptors that required DNA repair mechanisms for normal processing, thereby simultaneously providing the first genetic proof that TGF-β signaling was a tumor suppressor pathway and a mechanistic explanation for the appearance of colon cancer in Lynch Syndrome, which is associated with an inherited defect in DNA repair. We now know that one-third of all colon cancers are associated with alterations in TGF-β receptors, with or without concomitant defects in DNA repair mechanisms, and that different defects in TGF-β signaling are present in many other colon cancers.

Causation

In the last four years, we've finally been able to answer a key question that led from our initial discovery: What does TGF-β do in the gut that makes it so important as a tumor suppressor? Through a series of studies, we found that TGF-β metabolically suppresses an important oncogenic pathway, the cyclooxygenase 2 (COX2) pathway. COX2 is involved in inflammation; it is the target of drugs like aspirin and Celebrex. Interestingly, it has been known for many years that taking aspirin can lower the risk of colon tumors.

The gut also produces a naturally occurring inhibitor of the COX2 pathway, 15-hydroxyprostaglandin dehydrogenase (15-PDGH), which in turn is activated by TGF-β. Where COX2 promotes the synthesis of prostaglandins, 15-PDGH causes their degradation. Normally, 15-PDGH is strongly expressed in the gut; in colon cancers, this activity is downregulated. In disease models, we have shown that 15-PDGH can suppress tumor activity and that removal of 15-PDGH promotes vulnerability to tumors.

Moreover, people have individualized levels of 15-PDGH in the gut. Our collaborator, Monica Bertagnolli, M.D., at Brigham and Women's Hospital in Boston, led a clinical trial which demonstrated that Celebrex could reduce the recurrence of colon polyps by almost 50 percent. When we looked at the nonresponders, we found that they had low levels of 15-PDGH. We have now confirmed in similar studies with Andy Chan, M.D., Charlie Fuchs, M.D., and Shuji Ogino, M.D., Ph.D., that low levels of 15-PGDH are also associated with resistance to colon tumor prevention with aspirin. Thus, we have found a marker that is important in determining who would benefit from aspirin-type drugs as part of a tumor prevention strategy.

We are also beginning efforts to develop drugs that target the 15-PDGH pathway. Gratifyingly, that means we are once again working with Jim Willson, who moved from Case Western to the University of Texas (UT) Southwestern. UT Southwestern has made a significant investment in drug development infrastructure, recruiting Bruce Posner, Ph.D., to lead high-throughput screening, Joe Ready, Ph.D., to lead medicinal chemistry, and Noelle Williams, Ph.D., to lead pharmacology and formulation.

Early Detection

The importance of early detection has been strongly established for colon cancer. Through colonoscopies, we know that if you can catch it early, you can prevent death from the disease. But colonoscopies have been around since I was a medical student and colon cancer is still the second leading cause of cancer death in the United States. A few colon cancers are probably so aggressive they develop after screening, but many people simply do not get screened.

We've been developing non-invasive methods to detect colon cancer. A decade ago, a fellow in my laboratory, Bill Grady, M.D., (who now has his own lab at the Fred Hutchinson Cancer Center), found abnormally methylated DNA in the blood in about 15 percent of colon cancers. Five years ago, we did a genomic screen and found that the vimentin gene was methylated in about 80 percent of colon cancers. We've since shown that we may be able to detect up to 80 percent of early stage cancers (those that can be cured surgically) and even polyps by screening stool samples for this marker.

Methylated vimentin is part of a national multicenter trial to validate biomarkers for early detection against colonoscopies in 6,000 people through NCI's Early Detection Research Network. Through our GI SPORE, we are asking an associated question, namely what does it mean if a biomarker test is positive but the colonoscopy is negative? We've launched a clinical trial here at Case Western to follow people with positive stool tests and normal colonoscopies to see if the DNA test was right even though the lesion was not detected.

Translation

There is a gap that everybody recognizes and nobody yet knows how to fill between finding something in a lab that could actually have application as a therapy or diagnostic test and bringing it to clinical fruition. Capital, expertise, and commercial dedication are required to bring innovations through all the appropriate regulatory requirements. There are a few places in the country that have excelled at attracting venture capital for spinning companies out, but opportunities are often geographically confined.

This is particularly important now because research and development within Big Pharma is downsizing and, meanwhile, academia is generating fantastic opportunities. When I started out, I would have never guessed that we would be where we are now. The revolution in genetics and genomics and our ability to screen hundreds of thousands of compounds to find new drug leads is all beyond our wildest imaginings when I was in training. The possibilities still have a freshness and excitement to them that really make coming into the lab everyday a joy.